REMARKS

In view of the preceding amendments and the comments which follow, and pursuant to 37 CFR §1.111, amendment and reconsideration of the Official Action of June 7, 2005 is respectfully requested by Applicants.

The specification has been amended on page 1 to insert a specific reference to the prior application of which the present application is a continuation and to the parent application to which priority is claimed. Paragraph [0043] on page 10 has been deleted. Paragraph [0016] has been amended to insert the units shown on the Y-axis. Paragraphs [0026], [0032], and [0033] have been amended to change "high-molecular" to "high molecular weight". Finally, paragraph [0058] has been amended to clarify "reagent 2". Support for the language added to paragraph [0058] is found in paragraph [0063].

Claims 4 and 6-8 have been cancelled. Claims 1-3 have been amended. Support for the language "having a size from 10 nm to 300 nm" added to claim 1 is found in specification in paragraph [0025]. Support for the pH range amendment to claim 1 of 10.5 to 12.5 is found in the specification on page 7, paragraph [0030]. Support for the language "by chemical treatment" added to claims 2 and 3 is found in the specification in paragraph [0027]. No new matter has been added.

Claims 1-3 and 5 remain pending for examination.

Priority

The examiner has noted that a certified copy of the European application has not been filed. Concommitantly herewith, Applicants are filing a certified copy of EP 01118812.5.

Information disclosure statement

The examiner has noted several deficiencies in the information disclosure statement filed by Applicants on February 6, 2004. Among these are the Hermanson reference, wherein some of the listed pages were missing, some pages had obscured text, and the publication date and edition number were missing. Also, the Lagaly reference referred to on p. 17 of the specification was not listed on the information disclosure statement.

Applicants have submitted concurrently herewith a Supplemental IDS containing complete copies of the Hermanson and Legaly references. Applicants are aware, however, that the Legaly reference is only available in the German language and thus will not be considered by the examiner.

Restriction requirement

The examiner has required restriction of the claims to one of the following inventions:

Group I, claims 1-5, drawn to a method of making protein-coated polystyrene microparticles

Group II, claims 6 and 8, drawn to a polystyrene microparticle and a test kit for performing an immunoassay

Group III, claim 7, drawn to a method of detecting an analyte

Applicants confirm their provisional telephone election on May 16, 2005, of Group 1, claims 1-5, for examination. Applicants do not traverse the restriction requirement.

Objection to drawings

The examiner has objected to the drawings because the labels "Figure 1", etc., are not present and the label designating the Y-axis of the graph is not legible.

Applicants have submitted replacement drawings herewith that correct the deficiencies noted by the examiner, and they respectfully request the examiner's reconsideration.

Objection to specification

The examiner has objected to the specification because the text "high-molecular proteins" is ambiguous. Applicants have now amended their specification by changing all occurrences of that text to "high molecular weight proteins".

The examiner has also objected to the specification because paragraph [0043] refers to "boldface numbers" which are not present in either the examples or the drawings. Applicants have amended their specification by deleting paragraph [0043].

The examiner has also objected to the specification because the description of Figure 1 on page 4 does not include a description of the units of signal shown in the Y-axis of Figure 1. Accordingly, Applicants have amended paragraph [0016] on page 4 to insert the units for the Y-axis.

The examiner has also objected to the specification because on page 15, it is unclear what "reagent 2" is. Accordingly, Applicants have amended paragraph [0058] on page 15 to clarify "reagent 2".

The examiner's reconsideration of these objections to the specification is respectfully requested by Applicants.

Rejections under 35 USC §112, second paragraph

Claims 1-5 have been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1 has been rejected because the language "...a suspension of uncoated microparticles...the suspension comprising a buffer having a pH of 10.0 to 12.5" is indefinite because it suggests that the suspension of microparticles alone, prior to combination with protein, comprises a buffer of the recited pH. By way of the present amendment, Applicants have amended claim 1 in accordance with the examiner's suggestion to clarify that it is the final suspension which has a pH in the range of 10.0 to 12.5. It is not necessary that both the polystyrene particles as well as the protein are diluted in such buffer. It is only required that the final mixture has this pH.

Claim 1 has also been rejected because the recitation "...incubating the combination from (a) for a period of time whereby the protein is coated by adsorption onto the microparticles..." suggests that the protein is the species being coated and not the microparticles. Applicants have now amended claim 1 in accordance with the examiner's suggestion.

Claims 2 and 3 have been rejected because the recitation of proteins in "polymerized" form is unclear. Applicants have amended claims 2 and 3 to clarify that the protein is polymerized by chemical treatment.

Claim 4 has been rejected because the recitation "functionalized with epoxide groups" is indefinite. Applicants have now cancelled claim 4, thereby rendering the rejection moot.

Claim 5 has been rejected due to its dependence on an indefinite claim.

In light of the amendments to claims 1-3, the cancellation of claim 4, and the above remarks, the examiner's reconsideration of the rejection under 35 USC §112, second paragraph, is respectfully requested by Applicants.

Rejection under 35 USC §102 (b)

Claims 1, 2, and 4 have been rejected under 35 USC §102 (b) as being anticipated by Vaynberg et al., *Biomacromolecules 1*, 466-472, 2000 (hereinafter "Vaynberg") as evidenced by Bocquier et al., *Structure 7*, 1451-1460, 1999 (hereinafter "Bocquier"). The examiner argues that Vaynberg teaches a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation). The protein gelatin is a partner of a bioaffinity binding pair as it binds fibronectin (see "Bocquier") and the polystyrene latex used by Vaynberg is characterized as hydrophobic.

Applicants argue that Vaynberg does not disclose or anticipate the invention recited in claims 1 and 2 as amended (claim 4 having now been cancelled). The protein in Vaynberg, gelatin, is not a partner of a bioaffinity binding pair as required by claims 1 and 2.

Claims 1, 2, and 4 have been rejected under 35 USC §102 (b) as being anticipated by Jolley et al., J. Immunol. Methods 67, 21-35, 1984 (hereinafter "Jolley") as evidenced by Rembaum et al., U.S. Patent 3,957,741 (hereinafter "Rembaum"). The examiner argues that Jolley teaches a method for producing protein-coated polystyrene microparticles comprising the steps of combining a suspension of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair

(immunoreactive species, e.g., antigen), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation). Polystyrene latex has a hydrophobic surface as evidenced by Rembaum. Although Jolley does not specifically recite that the protein is coated by adsorption, this would inherently be the case when coating non-functionalized polystyrene microparticles at pH 10.

Applicants argue that Jolley does not disclose or anticipate the invention recited in claims 1 and 2 as amended (claim 4 having now been cancelled). Jolley teaches the

Claims 1, 2, and 4 have been rejected under 35 USC §102 (b) as being anticipated by Vinuesa et al., Langmuir 12, 3211-3220, 1996 (hereinafter "Vinuesa"). The examiner argues that Vinuesa teaches a method for producing protein-coated polystyrene microparticles comprising the steps of combining a suspension of uncoated microparticles, which may be hydrophobic, with a polymerized protein that is a member of a bioaffinity binding pair (Fab'_2), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by filtration).

Applicants argue that Vinuesa does not disclose or anticipate the invention recited in claims 1 and 2 as amended (claim 4 having now been cancelled). Applicants assert that the examiner's argument that Vinuesa teaches a microparticle coating method using a pH of 10 is in error.Vinuesa does teach a pH of 10; however that pH is used to perform surface charge density (Fig. 1) and electrophoretic mobility (Fig. 7) studies only. Other studies involving binding of protein to microparticles only involved pH's to 9.

In light of the amendments to claims 1-2, the cancellation of claim 4, and the above remarks, the examiner's reconsideration of the rejection under 35 USC §102 (b) is respectfully requested by Applicants.

Rejection under 35 USC §103 (a)

Claims 1 and 2 have been rejected under 35 USC §103 (a) as being unpatentable over Amiral et al., U.S. Patent No. 5,175,112 (hereinafter "Amiral"), in view of Steel et al., U.S. Patent No. 5,858,648 (hereinafter "Steel"). The examiner argues that Amiral teaches a method for producing protein-coated polystyrene microparticles substantially as claimed. The method includes the steps of combining a suspension of uncoated microparticles with a protein that is a member of a bioaffinity binding pair ("immunological substance"), the combination comprising a buffer of pH 10, and incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption. Amiral includes the step of rinsing the protein-coated microparticles but fails to specifically recite that the non-adsorbed protein is thereby separated from the protein-coated microparticles. However, Steel teaches a method for producing protein-coated polystyrene microparticles by adsorption that includes the steps of combining uncoated microparticles with a polymerized protein that is a member of a bioaffinity pair (toxoplasma and rubella antigens) in a suspension comprising a buffer of pH 9.6 and separating the non-adsorbed protein from the protein-coated microparticles by centrifugation. Steel teaches that the centrifugation of the coated microparticles is removing excess, i.e., unbound, antigen. It is the examiner's position that therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to include the centrifugation step as taught by Steel in the method for producing protein-coated polystyrene microparticles of Amiral because Steel teaches the benefit of centrifugation in removing excess antigen from the reaction mixture.

Applicants traverse the rejection and argue that the examiner's case for *prima facie* non-obviousness has not been made. Applicants argue that the combination of

references does not make the present invention and further, that Amiral teaches away from a combination with Steel. Neither Amiral nor Steel teach a pH in the range recited by claims 1 and 2. Amiral teaches ph 10, and Steel teaches pH 9.6. Moreover, Amiral teaches away from combination with Steel by teaching, at column 4, lines 3-20, that the choice of latex is of particular importance and that polystyrene particles, even when associated with a stabilizing material, are not stable with time. Amiral does not use a polystyrene particle as the examiner argues, but rather uses an acrylic latex consisting of styrene and butyl methacrylate units in a molar ratio of 40/60 to 45/55 styrene/butyl methacrylate (column 7, lines 1-4).

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claims 1 and 2 under 35 USC §103 (a) is respectfully requested by Applicants.

Claim 3 has been rejected under 35 USC §103 (a) as being unpatentable over Jolley in view of Tischer et al., U.S. Patent No. 5,061,640 (hereinafter "Tischer"). The examiner argues that Jolley teaches as described earlier but fails to teach a method for producing protein-coated polystyrene microparticles where the protein is a polymerized streptavidin. Tischer teaches a process for preparing a protein for binding to an insoluble carrier, and in particular, teaches polymerizing streptavidin by cross-linking, coupling the cross-linked streptavidin to a specifically bindable substance, and adsorbing the protein to polystyrene. Tischer further teaches that polymerizing proteins, including streptavidin, has the effect of increasing the molecular weights of the proteins, which results in improved adsorption to the insoluble carrier material. It is the examiner's position that therefore it would have been obvious to one of ordinary skill to employ polymerized streptavidin as taught by Tischer in the method for producing protein-coated microparticles of Jolley because Tischer teaches that polymerization of streptavidin results in improved adsorption to insoluble carriers, including polystyrene, and that this binding is stable with regard to detergents.

Applicants traverse the rejection and argue that the examiner's case for *prima facie* non-obviousness has not been made. Applicants argue that the combination of references does not make the present invention. Neither Jolley nor Tischer teach an adsorption pH in the range required by claim 3. Jolley teaches a pH range of 5.0 to 10.0; however, in Table I on page 28, Jolley teaches a decrease in performance of coated polystyrene latex particles with increasing pH, with particles at pH 10.0 showing the worst performance. Tischer fails to teach a pH for microparticle adsorption; however, in light of Jolley, one would be lead away from using a pH as high as 10 with the method of Tischer. Furthermore, claim 3 depends from claim 1 whose patentability is argued elsewhere herein, and claim 3 should enjoy the same patentability as claim 1.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claim 3 under 35 USC §103 (a) is respectfully requested by Applicants.

Claim 5 has been rejected under 35 USC §103 (a) as being unpatentable over Jolley in view of Bangs, Pure & Appl. Chem. 10, 1873-1879 (hereinafter "Bangs"). The examiner argues that Jolley teaches as described earlier but fails to teach microparticles that have a magnetizable core. However, Bangs teaches microparticles that have a magnetizable core and their utility in fast and easy separation of solid and liquid phases. It is the examiner's position that therefore it would have been obvious to one of ordinary skill to include the microparticles having a magnetizable core as taught by Bangs in the method for producing protein-coated polystyrene microparticles of Jolley because Bangs teaches the convenience of such microparticles in the fast and easy separation of solid and liquid phases in various assay types.

Applicants traverse the rejection and argue that the examiner's case for *prima facie* non-obviousness has not been made. Applicants argue that the combination of references does not make the invention of claim 5. Neither Jolley nor Bangs teach an adsorption pH in the range required by claim 5. Jolley teaches a pH range of 5.0 to 10.0;

however, in Table I on page 28, Jolley teaches a decrease in performance of coated polystyrene latex particles with increasing pH, with particles at pH 10.0 showing the worst performance. Bangs fails to teach a pH at all, it being rather a review article about particle-based immunoassays. Furthermore, claim 5 depends from claim 1 whose patentability is argued elsewhere herein, and claim 5 should enjoy the same patentability as claim 1.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claim 5 under 35 USC §103 (a) is respectfully requested by Applicants.

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3 and 5 at an early date is earnestly solicited.

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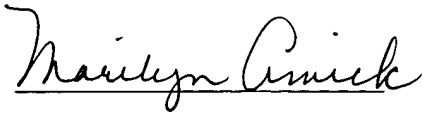
The examiner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 02-2958. A duplicate copy of this sheet is enclosed.

Respectfully submitted,



Marilyn L. Amick
Reg. No. 30,444

Customer No. 23690
Phone: 317-521-7561
Fax: 317-521-2883